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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,635	05/22/2001	Gerd Schmitz	Bayer 10,131-KGB	3503

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EXAMINER
MURPHY, JOSEPH F

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 09/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,635	SCHMITZ ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *7-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Formal Matters

Claim13 was added in Paper No. 10, 6/30/2003. Claims 1-13 are pending.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-6 in Paper No. 10, 6/27/2003 is acknowledged. The traversal is on the ground(s) that the claims all share the special technical feature of the nucleic acid which encodes SEQ ID NO: 2. This is not found persuasive because This is not found persuasive because CFR 1.475 (a) indicates that a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept. Where a group of inventions is claimed in an application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. CFR 1.475(e) indicates that the determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim (MPEP R-90 -- R-91 and 1893.03(d)). Applicant elected Group I, drawn to a nucleic acid encoding SEQ ID NO: 2, and polynucleotide fragments of the polynucleotide encoding SEQ ID NO: 2. In the instant case, the claimed polynucleotide is not a contribution over the prior art, see the rejections under 35 USC § 102(b), set forth below. Claims 1-6 are under consideration. Claims 7-13 are withdrawn from consideration pursuant to 37 CFR 1.142(b).

The requirement is still deemed proper and is therefore made FINAL.

Sequence Rules

According to 37 CFR 1.821(d) (MPEP § 2422), where the description or claims of a patent application discuss a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the assigned identifier, in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application. Sequences appear on page 37, lines 23-24 and page 39, line 13 to page 40 line 5 of the specification but are not identified by SEQ ID NO as required.

Appropriate correction is required.

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide encoding a polypeptide of SEQ ID NO: 2, or a polypeptide of SEQ ID NO: 2, does not reasonably provide enablement for a fragment of a polynucleotide encoding a polypeptide of SEQ ID NO: 2, or a fragment, analog or derivative of a polypeptide of SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue.

In the instant case, the claims are directed to a fragment of a polynucleotide encoding a polypeptide of SEQ ID NO: 2, or a fragment, analog or derivative of a polypeptide of SEQ ID NO: 2. Applicant has only taught SEQ ID NO: 1, encoding SEQ ID NO: 2. Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible muteins of ABCA1.

It is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. For example, Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous

individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Thus, the amino acid sequence of a polypeptide determines its structural and functional properties, and predictability of which amino acids can be substituted is extremely complex and well outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Since detailed information regarding the structural and functional requirements of the encoded proteins are lacking, it is unpredictable as to which encoding variations, if any, meet the limitations of the claims.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

These are genus claims. The claims are drawn to a fragment of a polynucleotide encoding a polypeptide of SEQ ID NO: 2, or a fragment, analog or derivative of a polypeptide of SEQ ID NO: 2. Applicant has only taught SEQ ID NO: 1, encoding SEQ ID NO: 2. Thus, the claims encompass methods using variant proteins. Applicant has only taught SEQ ID NO: 1, encoding SEQ ID NO: 2. The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. The specification and claim do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to SEQ ID NO: 2. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification and claims do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant one of skill in the art would

reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Claims 4-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a host cell in culture comprising a polynucleotide encoding SEQ ID NO: 2, does not reasonably provide enablement for in vivo transfection.

The claims encompass the nucleic acids of the current invention expressed in a wide variety of host cell types, including cells within a host animal. However, there are no actual or prophetic examples that disclose how to make or use host cells that comprise a DNA sequence encoding the polypeptide as set forth in SEQ ID NO: 2 in an animal. The Examiner cites Eck & Wilson (page 81, column 2, second paragraph to page 82, column 1, second paragraph) who report that numerous factors complicate *in vivo* gene expression which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. Since the instant disclosure does not address any of the methods necessary to make a host cell in an animal which comprises the polynucleotide of interest, the claims as written are not enabled. This rejection could be overcome by addition of the limitation wherein the host cells are isolated.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Luciani et al. (1994).

Luciani et al. teaches the cloning and expression of two members of the ATP binding cassette transporter family, ABC1 and ABC2. The nucleic acid encoding ABC1is more than 70% identical to a nucleic acid encoding SEQ ID NO: 2, and it would hybridize to SEQ ID NO: 2. For the sequence of the encoded protein, see Sequence Comparison A, attached. Luciani et al. teaches the cloning of the nucleic acid encoding ABC1 in a vector and the transfection of host cells with the nucleic acid (page 151, column 2, second and third paragraphs), thus claims 1-5 are anticipated. The ABC1 polypeptide comprises fragments of SEQ ID NO: 2, thus claim 6 is anticipated.

Claims 1-2, 6 are rejected under 35 U.S.C. 102(a) as being anticipated by Bodzioch et al. (1999).

Bodzioch et al. teaches Tangier Disease is caused by mutations in ABC1, encoding a member of the ATP-binding cassette (ABC) transporter family, located on chromosome 9q22-31. The polypeptide of the ABC1 transporter taught by Bodzioch et al. is 100% identical to the polypeptide of SEQ ID NO: 2 (see Sequence Comparison B, attached), thus claim 6 is anticipated. The polynucleotide encoding the ABC1 transporter would hybridize to the polynucleotide encoding SEQ ID NO: 2, and is at least 70% identical to SEQ ID NO: 2, thus claims 1-2 are anticipated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bodzioch et al. in view of Sibson et al. (WO/9401548).

The claims recite vectors and cells comprising the polynucleotide of the invention, as well as methods of producing proteins. As taught in the above rejection under 35 USC 102, Bodzioch et al. teach the claimed polynucleotide. Bodzioch et al. does not teach vectors and transformed cells comprising the polynucleotide of the invention, as well as methods of producing proteins. However, Sibson et al. do teach the use of vectors and cells to express DNA, as well as methods of producing proteins. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the invention of Sibson et al. by

substituting a cDNA in the polycloning region of the vector with the polynucleotide (cDNA) of Bodzioch et al. for the purpose of transfecting a host cell as taught by Sibson et al. in view of Sibson et al.'s suggestion that it would be desirable to do so (pages 8-13). One of ordinary skill in the art would have been motivated to make this substitution in order to express the protein encoded by the introduced DNA in a host cell to perform ligand binding and functional assays. There would have been a reasonable expectation of success for a person of ordinary skill in the art to make this invention since these techniques are widely used in the art and are highly successful (Sibson et al., page 10, line 38 - page 12, line 42). The present invention, therefore, is prima facia obvious over the above references in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph F. Murphy whose telephone number is 703-305-7245. The examiner can normally be reached on M-F 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
September 10, 2003

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